A comprehensive review on nutraceutical properties and pharmacological benefits for human healthcare in cocoa (Theobroma cacao L.)

Article *in* Annals of Phytomedicine An International Journal · January 2025

DOI: 10.54085/ap.2025.14.1.12

CITATIONS
0

READS
26

8 authors, including:

Kabilan .M
Tamil Nadu Agricultural University
31 PUBLICATIONS **6** CITATIONS
SEE PROFILE

Sundarrajan R. v.
Tamil Nadu Agricultural University
36 PUBLICATIONS **4** CITATIONS
SEE PROFILE

Thangamuniyandi Murugesan
Tamil Nadu Agricultural University
10 PUBLICATIONS **1** CITATION
SEE PROFILE

Annals of Phytomedicine 14(1): 115-127, 2025

DOI: http://dx.doi.org/10.54085/ap.2025.14.1.12

Annals of Phytomedicine: An International Journal
http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885

Review Article : Open Access

A comprehensive review on nutraceutical properties and pharmacological benefits for human healthcare in cocoa (*Theobroma cacao* L.)

J. Rajangam, M. Kabilan*, R.V. Sundarrajan◆, V. Raja**, M. Thangamuniyandi***, C. Sankar** and P. M. Usha Nandhini*****

Horticultural College and Research Institute, Periyakulam-625604, Theni, Tamil Nadu, India

** Division of Agricultural Chemistry, Regional Coffee Research Station, Coffee Board of India, Thandigudi-624216, Dindigul, Tamil Nadu, India*

*** Department of Fruit Science, Horticultural College and Research Institute, Periyakulam-625604, Theni, Tamil Nadu, India*

**** Department of Vegetable Science, Horticultural College and Research Institute, Periyakulam-625604, Theni, Tamil Nadu, India*

****** Department of Postharvest Technology, Horticultural College and Research Institute, Periyakulam-625604, Theni, Tamil Nadu, India*

Article Info

Article history
Received 17 March 2025
Revised 8 May 2025
Accepted 9 May 2025
Published Online 30 June 2025

Keywords
Theobroma cacao L.
Antihypertensive
Anti-inflammation
Antioxidant
Anticancer

Abstract

Cocoa is rich in several bioactive compounds, notably flavonoids such as catechins, epicatechins, and proanthocyanidins. These compounds exhibit strong antioxidant and anti-inflammatory properties, contributing to various health benefits. Additionally, cocoa contains methylxanthines like theobromine and caffeine, which can influence mood and cognitive function. Cocoa beans and cocoa-based products commonly include polyphenols. Consumption of products high in polyphenols, such as cocoa beans and their by-products, could assist in reducing inflammation and oxidative stress because polyphenols fight inflammation. Cocoa bean shells can serve as a useful ingredient or supplement in developing different and functional meals since they may contain valuable substances and nutrients like fibre, proteins, minerals, vitamins, and a wide range of polyphenols. Catechin, epicatechin enantiomers, procyanidin B2, and methylxanthines are among the flavonoids found in higher concentrations in cocoa. These characteristics suggest that chocolate may hold potential as a complementary agent in the treatment of colon cancer. Cocoa bean shells have long been recognised for their ethnopharmacological importance and have been used since the early days of traditional medicine. Due to their potential health benefits, they are being studied for possible pharmaceutical applications in managing various chronic diseases. A special focus has been placed on its cardiovascular benefits and anti-inflammatory qualities and its antiatherosclerosis, anticancer, antifertility, and antihypertensive qualities. More investigation is required to completely understand the mechanisms of action and establish suitable dosage guidelines for maximising cocoa's potential health advantages.

1. Introduction

The most significant and widely consumed nutritious food in the history of humanity originated from the fruit seeds of plant cocoa tree, *Theobroma cacao* L. (Malvaceae). Cocoa was first used by the Mayan and Aztec civilizations more than 3,000 years ago for dietary and medical purposes. Reaching 60% in both oligomeric (procyanidins) and monomer (epicatechin and catechin) forms is cocoa. Flavonoids typically comprise about 10% of the dry weight of cocoa powder, although this can vary depending on the production process. Colorectal cancer is expected to account for over 52,000 deaths annually; however, it is highly treatable when detected early, emphasizing the importance of regular screening and early intervention. United States, New Zealand, Canada, Australia, and other regions of Europe have the highest rates of colon cancer (Abarca *et al*., 2010). Colorectal cancer is widely believed to cause over 52,000 fatalities annually, but it is also highly treatable if detected early, underscoring the significance of testing for cancer in individuals. Colorectal cancer prevalence seems greatest in the United States, New Zealand, Canada, Australia, and several regions of Europe (Hernandez *et al*., 2019). Cancer is generally described as a multistage process involving three main phases: initiation, promotion, and progression. Cocoa, sourced from the dried and either fermented or unfermented seeds of *T. cacao*, boasts the highest flavanol content by weight. It plays a crucial role in overall flavonoid intake (Nas *et al*., 2017). Many people consume more cocoa products than other foods high in bioactive chemicals with comparable qualities, such as soybeans, wine, and tea with caffeine. Cocoa contains bioactive compounds, particularly flavonoids like epicatechin, which exhibit antioxidant properties that may influence insulin resistance and glucose metabolism. Plant-based products have been used for a long time as treatments for many medical conditions. These compounds have been shown to enhance insulin signalling pathways, such as PI3K/AKT and AMPK, in insulin-resistant liver cells, leading to improved glucose uptake and reduced glucose production. Additionally, cocoa flavonoids can activate redox-sensitive pathways, including Nrf2, promoting the expression of endogenous antioxidant defence genes and mitigating oxidative stress associated with type 2 diabetes. The portion of cocoa obtained from shell-free cocoa nib is referred to as a “cocoa component”; examples of such fractions include chocolate liquid, partially or fully defatted cocoa solids, cocoa extracts, cocoa butter and cocoa nib (Kofink *et al*., 2007). By

Corresponding author: Mr. R. V. Sundarrajan
Department of Fruit Science, Horticultural College and Research Institute, Periyakulam-625604, Theni, Tamil Nadu, India
E-mail: rvsun1999@gmail.com
Tel.: +91-9659033403

lowering the level of oxidative stress, eradicating viral infection, blocking cell development, and blocking or regulating metabolic processes, botanical medicines or phytonutrients were effective against liver disorders (Nadeem *et al*., 2022). The biologically active ingredients in chocolate products were related to multiple adverse effects. The antioxidant and anti-inflammatory properties of cocoa components are believed to be linked to several types of medicinal positive aspects, and consumption of chocolate and cocoa products has been associated in multiple epidemiological studies with a lower risk for serious diseases (Ellam *et al*., 2013). To elaborate, dietary supplements containing polyphenols have been employed as an adjunctive treatment measure.

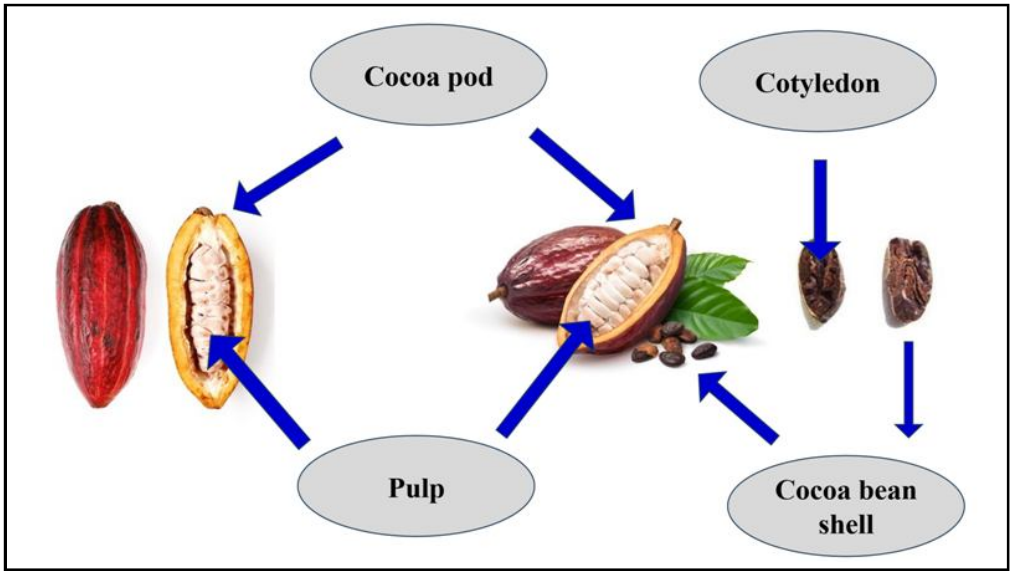

Figure 1: ***Theobroma cacao*** **L. fruit and foliage.**

For many years, chocolate was solely consumed for enjoyment, but studies conducted in the past 20 years have revealed that, because of their high polyphenol content, cocoa and dark chocolate may offer significant health benefits. Numerous preclinical investigations conclude that dietary polyphenols can have a positive effect when consumed in substantial amounts (Hu *et al*., 2007). This raises the knowledge of medical professionals by enabling whole foods to deliver nutrients and other beneficial components to different parts of the gut (Vaidya *et al*., 2022). The polyphenols found in cocoa, similar to those in green tea, are believed to exert beneficial effects on cardiovascular health, cholera, tuberculosis consumption, scarlet fever, smallpox, typhus, and yellow fever, as well as neurodegenerative diseases, changes in the lipid digestion system, inhibition of low-thickness lipoprotein (LDL) oxidation, reduction in the sequence of atherosclerotic injury, inhibition of platelet accumulation, decrease in the production of vascular cell grip atom, alter endothelial capacity, decrease in pulse, and anticancer activities shown in Figure 2.

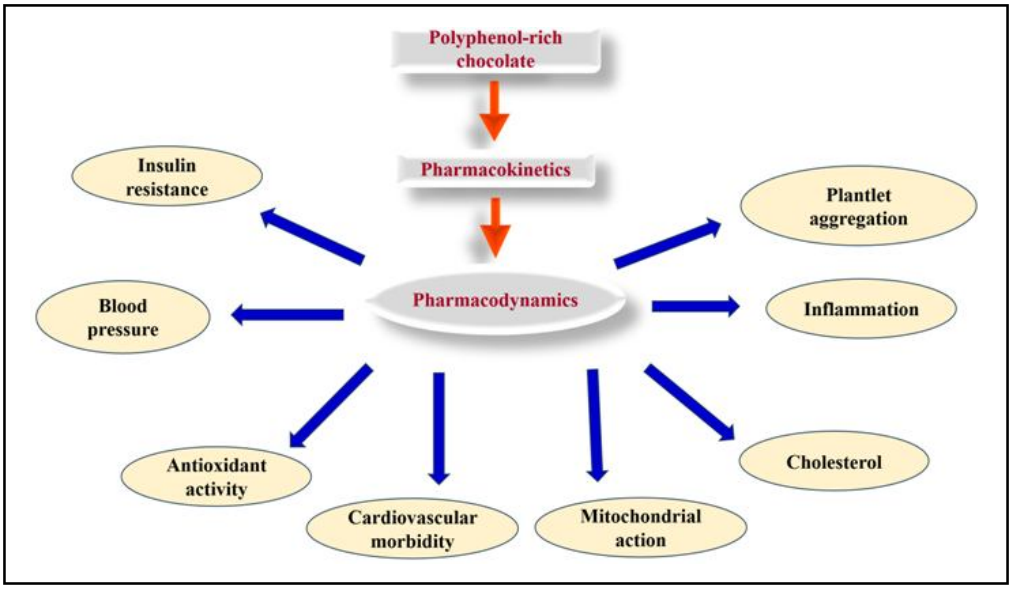

Figure 2: Effects of polyphenols on ***Theobroma cacao*** **L.**

2. Nutritional and chemical composition

The proximate composition of cocoa bean shells resembles the composition of cocoa beans and consists of proteins, lipids, carbohydrates, moisture, and ashes. In contrast, cocoa beans and cocoa bean shells have a significantly lower percentage of lipids but a significantly higher fibre content (Martin *et al*., 1994). In comparison to other cocoa by-products like cocoa pods, CBS also includes larger levels of proteins, lipids, and carbs (Perez *et al*., 2015). Agus *et al*. (2018) reported that the ash concentration in cocoa bean shells ranged from 5.96 to 11.42 g per 100 g, as shown in Figure 3. They observed that the concentration is modified by the roasting process, which raises it by around 15%. According to Osundahunsi *et al*. (2007), the principal elements in cocoa bean shell ash are sodium and potassium (7.2 and 3.1 g/100 g of ash, respectively). Studies on the protein composition have shown that proteins make up between 10.30% and 27.40% of the dried weight of cocoa bean shells. Some researchers have thought about using this by-product as a source of protein that can be extracted (Osundahunsi *et al*., 2007; Belscak *et al*., 2018). The complete amino acid profile of cocoa bean shells is 44.7%. D-amino acids, which constitute a small fraction of the total amino acid content in cocoa, tend to increase in proportion during roasting due to racemisation, a process influenced by heat, pH, and time. These D-isomers are generally less digestible than their L-counterparts, leading to reduced nutritional value. However, they play a significant role in flavour development during fermentation and roasting, contributing to the characteristic taste of cocoa products (Bonvehi *et al*., 1999; Chung *et al*., 2003). According to the literature, carbohydrates constitute 7.85-70.25 per cent of the dry weight of CBS, as shown in Table 1. Figure 3 shows that it varies widely depending on whether fibre content is included and since subtraction is frequently used to calculate them, adding to the unpredictability. For digestible carbohydrates, the cocoa bean shell is largely composed of available carbohydrates along with very little insoluble sugar, which has been deemed insignificant in certain studies (Martinez *et al*., 2012).

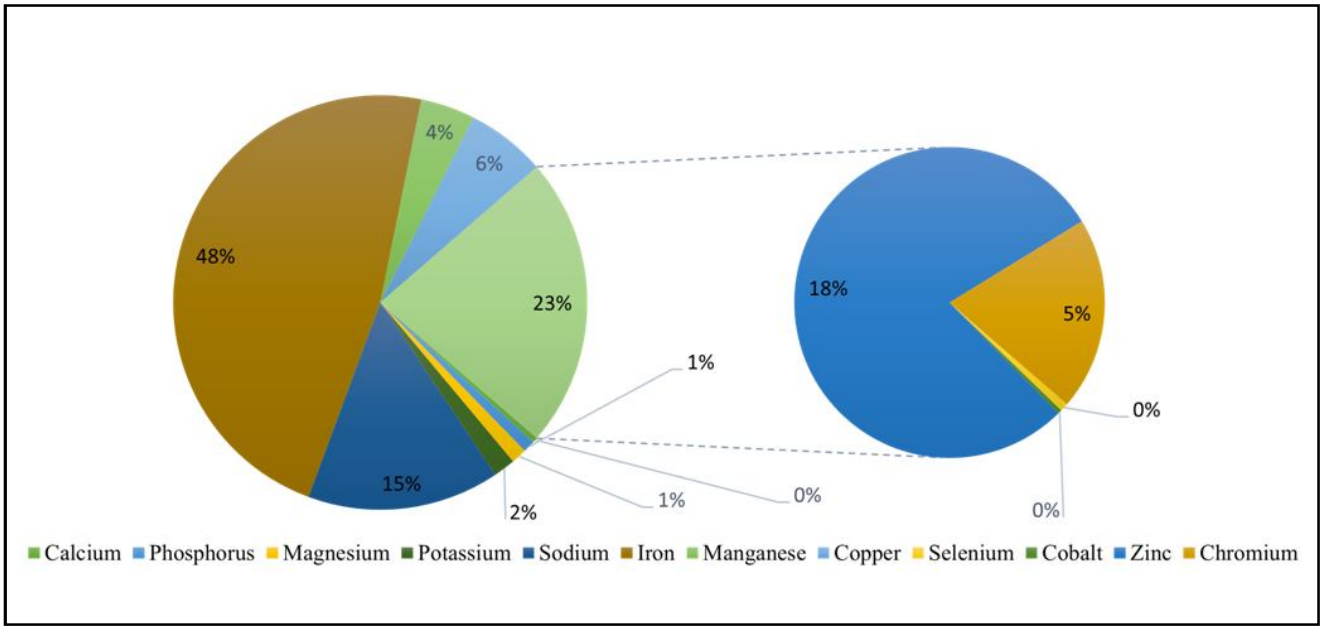

Figure 3: Nutraceutical composition of fruit pulp of *T. cacao*.

Table 1: Nutritional values of *Theobroma cacao* L.

S. No.	Parameter	Amount	References
1.	Ash (g/100 g)	5.96-11.42	Adamafio *et al*., 2013; Arlorio *et al*., 2001
2.	Carbohydrates (g/100 g)	7.85-70.25	Abarca *et al*., 2010; Belscak *et al*., 2018
3.	Soluble sugars (g/100 g)	0.16-1.66	Bonvehi *et al*., 1999
	Starch (g/100 g)	0-2.80	Martin-Cabrejas *et al*., 1994
4.	Dietary fibre (g/100 g)	39.25-66.33	Perez-Santana *et al*., 2018
	Insoluble fibre (g/100 g)	28.34-50.42	Lecumberri *et al*., 2007
	Soluble fibre (g/100 g)	7.03-16.91	Vojvodic *et al*., 2016
5.	Energy (kcal/100 g)	122.00	Rojo-Poveda *et al*., 2019
	Fats (g/100 g)	1.50-8.49	Vojvodi *et al*., 2016; Bonvehi *et al*., 1998; Belitz *et al*., 2009; Abarca *et al*., 2010)

6.	Flavanols		
	Catechin(mg/g)	0.18-4.50	Hernandez *et al*., 2019; Jokic *et al*., 2018; Papillo *et al*., 2019
	Epicatechin (mg/g)	0.21-34.97	
	Procyanidin B1(mg/g)	0.55-0.83	
	Procyanidin B2 (mg/g)	0.23-1.38	
7.	Methylxanthines		
	Caffeine (g/100 g)	0.04-0.42	Samanta *et al*., 2022; Cooper *et al*., 2008
	Theobromine (g/100 g)	0.39-1.83	
8.	Moisture (%)	3.60-13.13	Agus *et al*., 2018; Bonvehi *et al*., 1998; Rojo-Poveda *et al*., 2019
9.	Pectin (g/100 g)	7.62-15.59	Arlorio *et al*., 2001; Mollea *et al*., 2008; Nazaruddin *et al*., 2011; Chan *et al*., 2013
10.	Polyphenol content		
	Total flavonoid content	1.65-40.72	Nsor-Atindana *et al*., 2012; Lecumberri *et al*., 2007; Barbosa-Pereira *et al*., 2018
	Total phenolic content	3.12-94.95	
	Total tannin content	1.70-25.30	
11.	Proteins (g/100 g)	10.30-27.40	Ogunsipe *et al*., 2017; Sandoval *et al*., 2019
12.	Vitamins		
	B1 (µg/100 g)	0.70-3.10	Bonvehi *et al*., 1998
	B2 (µg/100 g)	0.90-3.10	
	B6 (µg/100 g)	0.52-2.52	
	D (µg/100 g)	0.25-0.53	Bonvehi *et al*., 1998; Knapp *et al*., 1935
	E (µg/100 g total tocopherols/g CBS fat)	1.02	Okiyama *et al*., 2019
	Volatile organic compounds (aromatics; µg/100 g)	4.92-16.10	Barbosa-Pereira *et al*., 2019

2.1 Dietary fibre

Dietary fibre is crucial to a healthy digestive tract because it helps with appropriate transit. The dietary fibre in CBS has several additional biological properties, including lowering lipid and glycerol levels inthe body, resulting in reduced risk of heart disease, and delaying the development associated with diabetes by slowing the absorption of glucose (Rusconi *et al*., 2010; Bonvehi *et al*., 1998). The structured carbohydrates, or non-starch polysaccharides, make up the dietary fibre of CBS. Because human enzymes cannot break down the remains of plant cell walls that make up this substance, it has no nutritional value. Various studies have outlined the methods used to determine CBS fibre content, revealing significant variations in the reported values. Gravimetric techniques are commonly employed within dietary fibre evaluation, as they include the non-starch polysaccharide fraction as well as "Klason lignin" fraction, which can occasionally be formed by complexes resulting from relationships between the tannin and amino acids and maillard process products along with lignin (Redgwell *et al*., 2003).

The by-product of cocoa processing is cocoa bean shells (CBS), which contain dietary fibre levels comparable to those found in cocoa pods. However, CBS distinguishes itself by having a higher proportion of soluble dietary fibre (SDF), which is associated with notable bio-functional properties. These properties include the potential to lower cholesterol levels, regulate blood glucose, and provide antioxidant benefits. The elevated soluble dietary fibre (SDF) content in CBS enhances its value as a functional ingredient in food products aimed at promoting health (Martinez *et al*., 2012). Several findings have focused on the pectin component of CBS fibre, which is mainly composed of galacturonic acid. This has been mainly due to its intriguing gelling capabilities, which are highly beneficial in industries including food, medicine, and cosmetics.

3. Bioactive compounds

T. cacao, the highly valued tropical plant used to produce chocolate, is also home to a multitude of bioactive chemicals that add to its appeal and possible health advantages. The study of these substances belongs within the field of phytochemistry and provides insight into the complex chemical makeup and biological functions of this well-liked plant.

3.1 Alkaloid

Cocoa naturally contains two primary alkaloids, theobromine and caffeine. Theobromine is present in higher concentrations than caffeine and is considered the main alkaloid in cocoa. While both compounds influence the central nervous system, caffeine is known for its strong stimulating effects, whereas theobromine exerts a milder influence. Theobromine primarily acts as a vasodilator and diuretic, with

minimal direct stimulation of the central nervous system. Despite its moderate effect, theobromine contributes to the mood-enhancing properties of chocolate, offering a subtle sense of well-being without the pronounced stimulation associated with caffeine (Zeng *et al*., 2022). Alkaloids add to the distinct flavour of cocoa and have been related to certain mood-boosting qualities, which enhance the enjoyment of consuming items made with cocoa. Alkaloids also improve the cardiovascular system by increasing blood flow and vasodilation (Nehlig, 2013).

3.2 Carotenoids

Antioxidant properties like carotenoids are commonly known as protecting cells from oxidative damage brought by free radicals. Although present in smaller amounts, carotenoids enhance the antioxidant capacity of cocoa, contributing to its potential health benefits. Although, carotenoids are less abundant in cocoa than other chemicals, they do play a role in the broad colour spectrum of cocoa beans. Beta-carotene represents a particularly significant carotenoid present in cocoa (Andarwulan *et al*., 2021).

3.3 Essential oils

Cocoa butter is a key product obtained from cocoa beans and the main ingredient in chocolate, serving as a significant source of essential oils. It has a distinct flavour and fragrance of cocoabelongs to these oils, which helps toimprove the sensory experience by consuming the products containing cocoa. Compared to certain aromatic plants, cocoa is lacking in large amounts of essential oil, but it contains small quantities of volatile molecules. Moreover, the essential oils had a major impact on the overall sensory appeal despite their very fragile presence (Edo *et al*., 2022). A major factor in the cultural and culinary appreciation of this prized commodity is the unique aroma and flavour of cocoa. The importance of the essential oils to the whole flavour experience should not be undervalued, even though they are not the main emphasis of cocoa.

3.4 Flavonoids

The polyphenolic compounds found in abundance in cocoa beans are known as flavonoids. Cocoa has different subclasses of flavonoids, such as procyanidins, epicatechins, and catechins. These compounds are distinguished by their complex molecular structures of molecules (Manju and Pushpa, 2020). Strong antioxidants and flavonoids play a vital role in fighting against oxidative stress and dangerous free radicals. Such as epicatechins and catechins not only provide major health advantages but also contribute to the bitter taste of cocoa (Nwosu *et al*., 2022). They have been linked to better cardiovascular health in part because reducing inflammatory processes while encouraging the arteries in the body to function normally. Another subclass of flavonoids included in cocoa, is procyanidins, having many cardiovascular advantages. Flavonoids, which are antioxidants, increase the total antioxidant properties of cocoa, highlighting the possibility of benefits to human health (Onyibe *et al*., 2021). Furthermore, studies on flavonoids, as well as a deeper comprehe nsion of their physiological effects with cocoa consumption may reveal even more important health consequences.

3.5 Glycosides

Glycosides are a class of chemicals in which an aglycone, a non-sugar component, is linked to a sugar molecule. Theobromine serves as the main glycoside which is found in chocolate. Theobromine is not as easily absorbed by the body as other glycosides. However, it releases the active theobromine during metabolism, which adds to the mildly stimulating effects of cocoa (Martinez-Pinilla *et al*., 2015). Vasodilatory effects of theobromine are well-known; they enlarge arteries and veins and may improve blood flow. Furthermore, it has modest diuretic properties that help the body get rid of extra fluid. Glycosides have attracted significant attention because of their possible health consequences. Glycosides contribute to the unique biochemical composition of cocoa, making it an interesting subject for scientific research (Soares and Oliveira, 2022).The prominent features of the obromine are its vasodilatory qualitieshelp to enlarge arteries, widening blood vessels, thereby improving the blood flow. Moreover, it also has slight diuretic properties, which help the body to get rid of extra fluid. Although, theobromine is a significant glycoside found in cocoa and because potential health effects. These compounds contribute to cocoa's unique biochemical profile, making it a compelling subject for scientific investigation.

3.6 Phytic acid

Phytic acid is a unique natural chemical found in plant seeds and the main functions as the primary type of phosphorus storage. It has received an enormous amount of attention because of its impact on mineral absorption. Phytic acid is sometimes referred to be an antinutrient since it prevents the absorption of iron, zinc, and calcium, potentially leading to mineral deficiencies (Akpoghelie *et al*., 2022). Moreover, Legumes, grains, nuts, and plant seeds all contain phytotic acid with a concentration of 0.98 g/100 g. Erhonyota *et al*. (2022) identified several methods that can be employed to lower the level of phytic acid in food, including soaking, sprouting, and fermentation. In addition to protecting against damage from oxidation and resistance to insulin, phytic acid may have other advantageous health effects. Phytate-rich foods may provide a risk to individuals who follow vegan or vegetarian diets or who consume large quantities of them (Edo *et al*., 2022).

3.7 Saponins

The saponins are a subclass of terpenoids, the largest group of plant extracts. Saponins are amphipathic, they can act as surfactants and interact with phospholipids and cholesterol in cell membranes, which could be useful in the production of pharmaceuticals and cosmetics (Hassan *et al*., 2021). The main function is an antifeedants and shield plants against bacteria and fungi. Certain plant saponins, such as those found in spinach and oats, help animals digest food better and absorb nutrients more readily. Since saponins typically have a bitter taste, they may potentially harm animals or make plants less appetizing when used in cattle feed. Certain saponins are toxic to insects and cold-blooded animals in certain amounts (Edo *et al*., 2022). Blood lipid levels, blood glucose response, and cancer risk are all decreased by saponins. Saponins are naturally occurring compounds found in a variety of plant-based foods and herbs. They are particularly abundant in legumes such as soybeans, chickpeas, lentils, kidney beans, and peanuts. Other notable sources include asparagus, spinach, onions, garlic, oats, tea leaves, ginseng roots, and liquorice. These compounds are recognised for their potential health benefits, including cholesterol-lowering effects and immune system support. However, it is important to note that saponin content can vary based on factors like plant species, growing conditions, and processing methods (Akpoghelie *et al*., 2022).

3.8 Terpenoids

Cocoa contains terpenoids in various amounts that may have a wide range of possible health advantages, although they are less investigated than other bioactive substances. According to Nwosu *et al*. (2022), these chemicals may have anti-inflammatory and antibacterial activities in addition to contributing to the distinctive flavour of cocoa. The significance of terpenoids in the composition of the bioactive chemicals in cocoa is highlighted by their possible involvement in boosting the body's defence mechanisms.

3.9 Phenolics

Phenolics, including procyanidins, flavonoids, and catechins, are a significant class of bioactive compounds in cocoa. These phenolic substances give cocoa its unique flavour and scent, which are essential to its antioxidant qualities (Melo *et al*., 2021). Cocoa beans contain aromatic compounds and antioxidant capacities that help protect the human body against damaging free radicals, reduce oxidative stress, and possibly lower the risk of several chronic illnesses, including heart conditions and some forms of cancer. These phenolic compounds are also linked to anti-inflammatory properties (Lee *et al*., 2003).

4. Phytochemical and medicinal uses

In addition to carbohydrates, the most interesting and studied components in CBS are polyphenols, which are also largely responsible for the biofunctional properties of the cocoa byproduct. These substances are found in all foods derived from vegetables and are widely known for generating a variety of biological actions. Flavonoids are a unique class of polyphenols, of which the major group in cocoa is flavanols (Wollgast and Anklam, 2000). Although they are not necessary for immediate well-being, accumulating research indicates that moderate long-term consumption of polyphenols may have various health advantages due to their antioxidant qualities, scavenge free radicals, and ability to lessen oxidative stress. They can participate in processes that have anti-inflammatory effects, antidiabetic effects, or lower the risk of several illnesses, including cancer, chronic illnesses, cardiovascular disease, and even neurodegenerative disorders (Vauzour, 2014; Hussain *et al*., 2016: Rodriguez-Mateos *et al*., 2014). Approximately 422 million individuals globally suffer from diabetes, with the majority residing in low and middle-income nations. The disease is directly accountable for the 1.5 million fatalities that occur each year. In the previous decades, there have beeninstances of ongoing increase in both the number of cases and the incidence of diabetes. Natural supplements and herbal medicines featuring fewer side effects are being proven as possible diabetes treatments that may enhance patient quality of life (Sanjeev *et al*., 2021)

4.1 Cocoa nutshell

Cocoa shells may also provide health benefits for people with excessive cholesterol and this product was rich in soluble dietary fibre and contained significant amounts of antioxidant polyphenols. Additionally, it reduced lipid peroxidation, which in turn reduced a number of cardiovascular disease risk factors. The nutritional benefits of cocoa bean shells have also been shown since they lower food intake and body weight growth. (Perez-Santana *et al*., 2018) present another study that demonstrates the possibility of soluble dietary fibre.

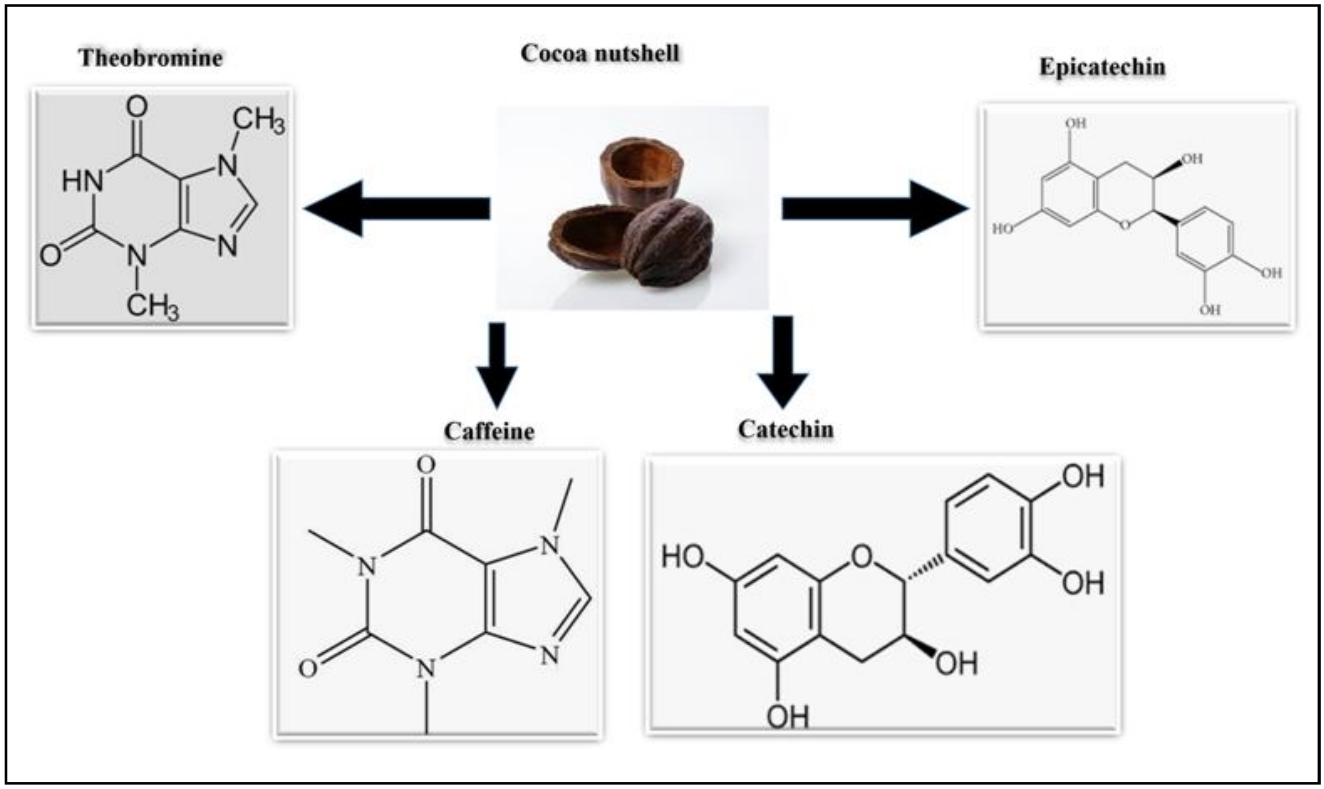

Figure 3: Flavonoids and alkaloid compounds in *Theobroma Cacao* L. nutshell.

4.2 Cocoa leaves

It is possible that cocoa leaves could be turned into more beneficial dietary items. Thus, it is essential to make additional use of plantation residue in the form of cocoa leaves, for example, by turning them into herbal tea. Antioxidants play a crucial role in reducing the impact of free radicals, which are intrinsically linked to the development of degenerative diseases that stem from metabolic processes within the body. The chemical components found in cocoa leaves include alkaloids (particularly theobromine) and flavonoids (particularly catechins). Bioactive compounds termed flavonoids and alkaloids, which can donate hydrogen atoms or bind metals to act as antioxidants, can take the form of glucosides (which contain side chains of glucose) or free-form molecules known as aglycones. Cocoa leaves also include theobromine, caffeine, anthocyanins, leuco-anthocyanins, and catechol, with different proportions based on the leaf's age, shown in Figure 4. Alkaloids, flavonoids, tannins, saponins, steroids, and glycosides are among the classes of substances are also identified by utilizing phytochemical screening techniques in cocoa leaves (Rani *et al*., 2021).

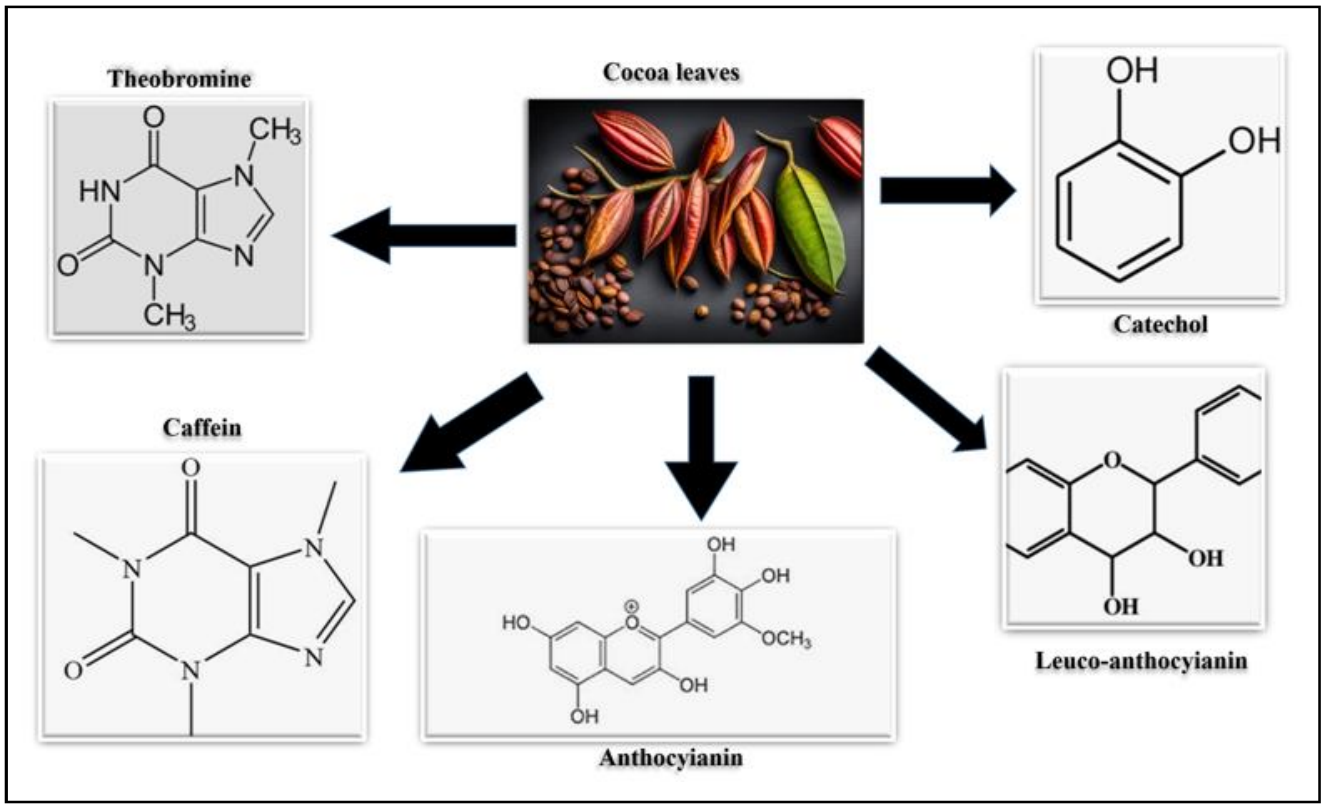

Figure 4: Flavonoids and alkaloid compounds in leaves of *Theobroma Cacao* L.

5. Biological activities of cocoa

The edible portion of cocoa beans has been proven to have numerous health advantages and primarily due to its high polyphenol content and flavonoids. As was previously noted, a lot of research has indicated that these cocoa phytochemicals give cocoa products many functionalities, like anticancer activity (Martin *et al*., 2013). Affects diabetes, a condition advantageous to cardiovascular health, implications for neurodegenerative illnesses, antibiotic activity, or characteristics of inflammatory mediators. Furthermore, cocoa bean polyphenols are particularly well-known for their unique structures that mimic multiple inhibitors and receptor agonists or inhibitors of various cellular signalling pathways because of the presence of anti-inflammatory properties (Daglia *et al*., 2012; Sies *et al*., 2005). In recent years, more specifically, many studies have suggested potential advantages of cocoa bean shell and its by-product in the food and pharmaceutical industries. More particularly, it has been noted that antibacterial and antiviral qualities protect against cardiovascular illnesses in addition to they also have anticarcinogenic, antidiabetic, neuroprotective, and anti-inflammatory actions. The mode of action for the functionalities is described in Table 2.

5.1 Antiatherosclerotic activities

Inflammatory illness of the arterial vascular wall is the commonly recognised theory of atherosclerosis in recent years. To create an atherosclerotic fibrous plaque, inflammation must occur in the complex processes of cell migration and extracellular matrix (ECM) synthesis. Plaque disruption at later phases of extracellular matrix breakdown results in clinical atherothrombotic disorders (Barbosa *et al*., 2018). The extracellular matrix's (ECM) breakdown within a normal vessel wall is regulated by the interaction of proteinases and their endogenous inhibitors. However, the production of several proteinases, including matrix metalloproteinases (MMPS), the concentration of macrophages, and phenotypically altered vascular smooth muscle cells (VSMCS) could tip the balance toward matrix degradation at locations susceptible to fibrous cap rupture. These inhibitory effects were explained as the result of the kinase MEK1

directly inhibiting MT1-MMP, a particular membrane-bound MMP. It is noteworthy that red wine polyphenols, which are well-known for having a beneficial impact on cardiovascular health, did not show the same inhibitory effects as procyanidin B2 and CPF.

Thrombin is a multifunctional serine protease that causes proinflammatory reactions in the cells of endothelial cells and VSMC, activating thrombin and MMPs and converting fibrinogen to fibrin, all of which greatly contribute to vascular injury. It is a potent inducer of MMP-2 in both cell types andit was discovered that MT1-MMP, the first MMP linked to the cell membrane, mediates cell migration and several inflammatory events (Okiyama *et al*., 2018).

5.2 Anticancer activities

Further studies and growing interest in the potential anticancer properties of cocoa offer promising prospects for its role in cancer prevention and treatment (Martin *et al*., 2016). Research on cocoa's bioactive ingredients is still in its infancy, but investigations conducted on animals and in laboratories have revealed promising results about its flavonoids and other polyphenols. According to Goya *et al*. (2022), one of the main ways that the bioactive chemicals in cocoa may have an anticancer effect is by functioning as an antioxidant. Flavonoids, substances that are common in cocoa and are well-known for their beneficial antioxidant potential, include epicatechins and catechins. These antioxidants can protect against dangerous free radicals, which are unstable molecules that can damage cells and have a role in the emergence of cancer. Antioxidants found in cocoa can protect tissues against damage and minimise damage caused by oxidative stress, which may help delay or stop the development and spread of cancer. Cocoa contains bioactive compounds, particularly flavonoids like catechins and epicatechins, which exhibit both antioxidant and anti-inflammatory properties. These properties may contribute to modulating the body's inflammatory response, potentially reducing the risk of cancer development and progression. Chronic inflammation is associated with an increased likelihood of cancer growth and spread, and the anti-inflammatory effects of cocoa flavonoids may help mitigate this risk (Ahmed *et al*., 2020). Moreover, studies have looked into the potential of several cocoa-derived chemicals to control the cellular cycle, known as the process by which cells divide, grow, and eventually die (Baranowska *et al*., 2020). Since cancer cells frequently avoid the regular checks and balances that regulate cell proliferation, abnormal cell cycle regulation is a defining feature of cancer. The biologically active elements of cocoa may aid in managing the cell cycle, halting unchecked cell division and averting the development of tumours. The capacity of cocoa to cause cancerous cells to undergo apoptosis is an additional fascinating feature of its possible anticancer properties. Apoptosis is a normal process of planned cell death that helps maintain tissue homeostasis (Subramaniam *et al*., 2019). Cancer cells frequently avoid dying, which promotes unchecked cell division and the development of tumours. The bioactive components of cocoa may cause cancer cells to undergo the process of apoptosis, which would cause them to self-destruct and stop growing tumours. Furthermore, research has been done on the possible antiangiogenic properties of cocoa. Cancer requires angiogenesis, or the creation of fresh blood vessels, to proliferate and spread. According to certain research, the flavonoids found in cocoa may prevent angiogenesis, which might reduce the blood flow to tumours and impede their growth (Saman *et al*., 2020). It is critical to consider cocoa as a component of a healthy diet and way of life rather than as a stand-alone cancer treatment.

The anticancer effects of cocoa and its main flavanols have been investigated, allowing for the clarification of their molecular mechanisms of action (Table 3). These studies have collectively shown that the mechanisms behind the potential chemopreventive impact of cocoa and its flavonoids are mainly linked to their antioxidant and anti-inflammatory properties, as well as their ability to inhibit cell division and induce apoptosis. Furthermore, no studies have been done with HT-29 cells among the "standard" colon cancer cell lines (Rossin *et al*., 2019).

5.3 Antifertility activities

Cocoa beans contain theobromine, a chemical compound that hasa subtle stimulant quality. Theobromine, as well as caffeine, maintains a structural relationship, however, the compound's effects on the reproductive system are better researched and more noticeable than the latter. High theobromine dosages have been linked in certain research on animals to decreased fertility and negative effects on reproductive organs (Cappelletti *et al.,* 2015). Hence, it is important to take the antifertility properties of cocoa cautiously, and additional study is required to completely comprehend its ramifications. Research has indicated that specific components included in cocoa, like theobromine, could impact sperm quality and hormone production (Gabrielsen *et al.,* 2016). These trials, however, frequently used dosages that were far larger than those that one would normally take from dietary sources. However, some research indicates that a modest cocoa intake could not deleteriously impact fertility. The cocoa has been consumed historically for generations across a wide range of cultures without seeming to have any deleterious effects on reproductive health. It is important to understand that everyone's experience with the effects of cocoa on fertility is different and that individual variances, dosage, and duration of consumption can all affect how the food may affect reproductive health. It is also critical to distinguish between products that include cocoa and those that consume it. Although, natural cocoa beans include a variety of bioactive components, products made with cocoa, like chocolate, may also contain other elements like sugar and lipids, which have an impact on fertility and general health (Rojo-Poveda *et al.,* 2019).

5.4 Antihypertensive activities

Clinical research on cocoa's effects on blood pressure highlights the importance of comparing flavanol doses, rather than focusing solely on the quantity of chocolate or cocoa products consumed (Martinn *et al.,* 2016). Traditionally, indigenous people of Latin America drank cold, unsweetened beverages prepared from raw, dried cocoa powder, frequently mixed with flour and spices (Perez *et al.,* 2015). Fresh and fermented cocoa beans have a flavanol level of approximately 10% (100 mg/g), but dark chocolate that is sold in stores normally has a flavanol content of only 0.5%. Research has indicated that the beneficial impacts of cocoa on blood pressure are related to the generation of endothelial nitric oxide (NO), which encourages vasodilation and lowers blood pressure. Cocoa flavanols also contribute to the antihypertensive qualities of cocoa by inhibiting the production of the angiotensin-converting enzyme (ACE), which improves insulin sensitivity and cardiovascular health (Reed, 2020). The antisickling benefits of *T. cacao* extract from Cameroon'slittoral and southwestern areas were investigated. Assessments of the activities of catalase, SOD, glutathione peroxidase, reduced glutathione, and malondialdehyde contribute to the investigation of *T. cacao* antioxidant potential. Further research was conducted on

the extracts antisickling properties, osmotic fragility tests, and principal component analysis (PCA). Focusing on the cocoa extract, these extracts also exhibit incredibly potent antiradical activity against the DPPH and ABTS radicals, with IC_{50} values varying from 4.87 to 19.29 g/ml and 3.24 to 6.35 g/ml, respectively. According to the PCA results, cocoa extract was better able to prevent haemolysis, lessen sickling, and regulate enzyme activity when stress was induced (Rodriguez-Ramiro *et al*., 2013). These findings indicate that infection may be treated by using cocoa bean extracts from these areas. The application of cocoa in the treatment of sickle cell anaemia has gained interest due to its antisickling properties and additional beneficial biological activities.

Table 3: Effects of cocoa and cocoa flavonoids on colonic cancer

S. No.	Flavonoid	Cell	Biological activity	Output	Reference
1.	Cocoa	Caco-2	Antioxidant	acrylamide-incubated cells: ↓ GSH depletion, ROS generation, ↑ γ-GCS, ↑ GST	Rodriguez *et al*., 2011
			Anti-inflammatory	↓ PGE2, ↑ COX-1, IL-stimulated cells: ↓ PGE2, =IL-8, =NF-κB.TNF-treated cells: ↓ IL-8, ↓ COX-2, ↓ iNOS, ↓ NFκB activation	Romier *et al*., 2009; Rodriguez-Ramiro *et al*., 2011
2.	Catechin	Int-407	Antioxidant	↓ lipid peroxidation, ↓ ROS formation, ↑ GPx, ↑ GR, ↑ Nrf2, ↑ HO-1	Cheng *et al*., 2013
3.	Epicatechin	Caco-2	Antioxidant	*t*-BOOH- treated cells: ↓ ROS generation, ↓ LDH, =GPx, =GST, =GR,acrylamide- incubated cells: ↓ GSH depletion, ↓ ROS generation	Rodriguez - Ramiro *et al*., 2013
			Apoptosis and proliferation/ survival	↓ *t*-BOOH-induced caspase-3	
		LoVo	Cell cycle	S arrest	Tan *et al*., 2000
4.	Hexamer procyanidins	Caco-2	Antioxidant	t-BOOH-treated cells: ↓ ROS generation, ↓ LDH ↓ DOC-induced cytotoxicity, ↓ oxidant generation, ↓ NADPH oxidase, ↓ Ca^{2+}	Da silva *et al*., 2012; Erlejman *et al*., 2008
			Anti-inflammatory	TNF-treated cells: ↓ NF-B activation (↓ p-IkB, ↑ IkB, ↓ p50 and p65 translocation, ↓ NF-B-DNA binding), ↓ iNOS	Erlejman *et al*., 2008
5.	Polymer procyanidins	Caco-2	Cell cycle	G2/M arrest, ↓ ornithine decarboxylase, ↓ S-adenosyl methionine decarboxylase	Carnesecchi *et al.,* 2002
6.	Procyanidin B2	Caco-2	Antioxidant	acrylamide-incubated cells: ↓ GSH depletion, ↓ ROS generation, ↑ γ-GCS, ↑ GST	Rodriguez-Ramiro *et al.,* 2011

5.5 Anti-inflammatory activities

Cocoa beans are rich in bioactive compounds, notably flavonoids and polyphenols, which contribute to their anti-inflammatory properties. These compounds can modulate inflammatory responses by influencing signalling pathways and reducing pro-inflammatory mediators (Nehlig *et al*., 2013). Prolonged inflammation is linked to several chronic diseases, such as cardiovascular diseases, neurodegenerative disorders, and some types of cancer. Cocoa's bioactive compounds, particularly flavonoids, are believed to modulate the body's inflammatory response and reduce excessive inflammation (Rudrapal *et al*., 2022). The anti-inflammatory properties of flavonoids, which are abundant in cocoa and include epicatechins and catechins, have been thoroughly investigated. It has been demonstrated that these substances suppress the synthesis and function of pro-inflammatory molecules, including prostaglandins and cytokines, which playa key role in the inflammatory process. (Al-Khayri *et al*., 2022) state that the flavonoids in cocoa aid in reducing inflammatory reactions in the body by lowering the amounts of these pro-inflammatory chemicals. The bioactive substances in cocoa may also have antioxidant properties, scavenging free radicals and lowering oxidative stress. The antioxidants in cocoa may indirectly contribute to its anti-inflammatory properties by lowering inflammation, which can be triggered by oxidative stress. Cardiovascular health is especially affected by the anti-inflammatory properties of cocoa. Atherosclerosis, a disorder marked by the accumulation of plaque in blood arteries, is largely caused by chronic inflammation. The bioactive components in cocoa support normal blood vessel function and enhance cardiovascular health by lowering inflammation. Furthermore, there may be anti-inflammatory benefits of cocoa for brain function. Neurodegenerative conditions such as Parkinson's and Alzheimer's disease are associated with inflammation. The bioactive components of cocoa may have neuroprotective effects by reducing inflammatory reactions, which could enhance cognitive

performance and brain health. Despite the encouraging data, caution should be exercised in conducting further studies on the anti-inflammatory properties of cocoa. To completely comprehend the scope and clinical significance of cocoa's anti-inflammatory benefits in humans, additional clinical trials involving human subjects are required, as the majority of investigations have been carried out in lab settings or animal models (Cheng *et al*.,2013). Numerous medications, including immunosuppressants and nonsteroidal anti-inflammatory agents, are available on the market to reduce or combat this kind of inflammation. Use the lowest effective dose of certain medications because prolonged use can cause side effects (Rahul *et al*., 2023). Furthermore, it is best to take cocoa-based products in moderate amounts, especially those that have additional sugars and fats, as excessive consumption may have negative health effects, such as possible weight gain and dental problems.

5.6 Antimicrobial activities

The antimicrobial benefits of cocoa beans are still being researched and analysed by scientists. Certain biologically active substances found in cocoa have demonstrated possible antimicrobial properties against a range of microorganisms, including viruses, bacteria, and fungi (Nsor-Atindana *et al*., 2012). Theobromine is one of the main bioactive components of cocoa beans that has antimicrobial properties. It is an alkaloid found in cocoa beans that gives cocoa mild stimulating effects. Research has shown that theobromine has some degree of antimicrobial activity, especially against some bacteria,whichprevents the growth of some oral bacteria linked to periodontal disease and dental caries. Theobromine's antimicrobial activity is generally weaker than that of traditional antimicrobial agents used in medicine. Furthermore, from theobromine, cocoa also contains other substances that could be involved in its antimicrobial properties. According to the research, procyanidins and catechins, two flavonoids included in cocoa, may have antibacterial qualities (Nsor-Atindana *et al*., 2012). These flavonoids are involved in the antibacterial properties of cocoa since they have shown inhibitory effects against a variety of bacteria and viruses. Although, the antibacterial properties of cocoa are not advisable solely to treating or preventing illnesses. Rather, they enhance cocoa's allure as a meal that may be good for health (Akpoghelie *et al*., 2022). Nowadays, the use of goods coated with nanoparticles is used in dentistry because of the benefits of the materials. According to Sreenivasagan *et al*. (2020), silver nanoparticles are specifically being used in a variety of dental products due to their antibacterial qualities.

5.7 Antioxidantactivities

Antioxidants are essential for the body because they counteract the damaging effects of free radicals. Unstable chemicals known as free radicals have the potential to damage cells and cause oxidative stress, which is linked to several chronic illnesses and the ageing process. This oxidative stress can cause inflammation and damage cells if not controlled. The antioxidant properties of cocoa beans have been verified by numerous studies (Martin *et al*., 2016). According to a study; for example, intake of chocolate raises haemoglobin levels of antioxidants, there by increases the overall levels of antioxidants. Reductions of oxidative stress in the body have also been linked to the regular use of cocoa-based products. Additionally, studies have indicated that cocoa's antioxidants may be able to fend off a range of chronic illnesses. Because cocoa contains antioxidants that may support cardiovascular health and preserve the normal function of arteries, studies have suggested that consuming cocoa may lower the risk of cardiovascular illnesses (Nsor-Atindana *et al*., 2012). Further research has revealed significant advantages for brain health and thinking capacity because of the neuroprotective properties of cocoa antioxidants.

6. Conclusion

Cocoa has a wide range of biological activity and possible health advantages due to its abundance of bioactive substances, such as flavonoids and phenolics. It may help to improve brain function and cardiovascular fitness because of its anti-inflammatory and antioxidant qualities. It has interesting potential because of its antibacterial properties and emerging indications of possible anticancer effects. Further study is required to completely research on the bioactive compounds in cocoa is still in its early stages. Studies conducted in laboratories and on animals have shown encouraging findings regarding its flavonoids and other polyphenols. While cocoa-based products offer potential health benefits, they should still be consumed in moderation as part of a balanced diet.

Acknowledgments

The authors express their sincere gratitude and credit the researchers behind the original studies whose works are referenced in this review.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

Abarca, D.; Martinez, R.; Munoz, J. J.; Torres, M. P. and Vargas, G. (2010). Residuos de café, cacao y cladodio de tuna: Fuentes promisorias de fibra dietaria. Revista Tecnoligica-Espol, **23**(2):63-69. DOI: 10.37815/rte

Adamafio, N.(2013). Theobromine toxicity and remediation of cocoa by-products: an overview. Journal of Biological Science, **13**(5):570-576.

Agus, B. A. P.; Mohamad, N. N. and Hussain, N. (2018). Composition of unfermented, unroasted, roasted cocoa beans and cocoa shells from Peninsular Malaysia. Journal of Food Measurement and Characterization, **12**(6):2581-2589. https://doi.org/10.1007/s11694-018-9875-4

Ahmed, S.; Ahmed, N.; Rungatscher, A.; Linardi, D.; Kulsoom, B. and Innamorati, G. (2020). Cocoa flavonoids reduce inflammation and oxidative stress in a myocardial ischemia-reperfusion experimental model. Anti-oxidants, **9**(2):167. https://doi.org/10.3390/antiox9020167

Akpoghelie, P. O. and Edo, G. I. (2022). Proximate and nutritional composition of beer produced from malted sorghum blended with yellow cassava. Biocatalysis and Agricultural Biotechnology, **45**(9):102535. https://doi.org/10.1016/j.bcab.2022.102535

Al-Khayri, J. M.; Sahana, G. R.; Nagella, P.; Joseph, B. V.; Alessa, F. M. and Al-Mssallem, M. Q. (2022). Flavonoids as potential anti-inflammatory molecules: A review. Molecules, **27**(9):2901. https://doi.org/10.3390/molecules27092901

Andarwulan, N.; Cahyarani Puspita, N.; Saraswati, N. and Srednicka-Tober, D.(2021). Antioxidants such as flavonoids and carotenoids in the diet of Bogor, Indonesia residents. Antioxidants, **10**(4):587. https://doi.org/10.3390/antiox10040587

Arlorio, M.; Coisson, J. D.; Restani, P. and Martelli, A. (2001). Characterization of pectins and some secondary compounds from Theobroma cacao hulls. Journal of Food Science, **66**(5):653-656. https://doi.org/10.1111/j.1365-2621.2001.tb04616.x

Baranowska, M.; Suliborska, K.; Todorovic, V.; Kusznierewicz, B.; Chrzanowski, W.; Sobajic, S. and Bartoszek, A. (2020). Interactions between bioactive components determine antioxidant, cytotoxic and nutrigenomic activity of cocoa powder extract. Free Radical Biology and Medicine, **154**(12):48-61. https://doi.org/10.1016/j.freeradbiomed. 2020.04. 022

Barbosa-Pereira, L.; Guglielmetti, A. and Zeppa, G. (2018). Pulsed electric field assisted extraction of bioactive compounds from cocoa bean shell and coffee silverskin. Food and Bioprocess Technology,**11**(12):818-835. https://doi.org/10.1007/s11947-017-2045-6

Barbosa-Pereira, L.; Rojo-Poveda, O.; Ferrocino, I.; Giordano, M. and Zeppa, G. (2019). Analytical dataset on volatile compounds of cocoa bean shells from different cultivars and geographical origins. Data in Brief, **25**(10):104-268. https://doi.org/10.1016/j.dib.2019.104268

Belitz, H. D.; Grosch, W. and Schieberle, P. (2009). Coffee, tea, cocoa. Food Chemistry, **12**(2):938-970. https://doi.org/10.1007/978-3-540-69934-7_22

Belscak-Cvitanovic, A.; Vojvodic, A.; Busic, A.; Keppler, J.; Steffen-Heins, A. and Komes, D. (2018). Encapsulation templated approach to valorization of cocoa husk, poppy and hemp macrostructural and bioactive constituents. Industrial Crops and Products, **112**(6):402- 411. https://doi.org/10.1016/j.indcrop.2017.12.020

Bonvehi, J. S. and Coll, F. V. (1999). Protein quality assessment in cocoa husk. Food Research International, **32**(3):201-208. https://doi.org/10.1016/S0963-9969(99)00088-5

Bonvehi, J. S. and Jorda, R. E. (1998). Constituents of cocoa husks. Zeitschrift für Naturforschung C, **53**(9):785-792.

Cappelletti, S.; Daria, P.; Sani, G. and Aromatario, M. (2015). Caffeine: Cognitive and physical performance enhancer or psychoactive drug. Current Neuropharmacology, **13**(1):71-88

Carnesecchi, S.; Schneider, Y.; Lazarus, S. A.; Coehlo, D.; Gosse, F. and Raul, F. (2002). Flavanols and procyanidins of cocoa and chocolate inhibit the growth and polyamine biosynthesis of human colonic cancer cells. Cancer Letters, **175**(2):147-155. https://doi.org/10.1016/S0304-3835(01)00731-5

Chan, S. Y. and Choo, W. S. (2013). Effect of extraction conditions on the yield and chemical properties of pectin from cocoa husks. Food Chemistry, **141**(4):3752-3758. https://doi.org/10.1016/j.foodchem. 2013.06.097Get rights and content

Cheng, Y. T.; Wu, C. H.; Ho, C .Y. and Yen, G. C. (2013). Catechin protects against ketoprofen-induced oxidative damage of the gastric mucosa by up-regulating Nrf2 *in vitro* and *in vivo*. The Journal of Nutritional Biochemistry, **24**(2):475-483. https://doi.org/10.1016/j.jnutbio. 2012.01.010

Chung, B. Y. and Han, K. W. (2003). Compositional characterization of cacao (*Theobroma cacao* L.) hull. Journal of Applied Biological Chemistry, **46**(1):12-16.

Cooper, K. A.; Donovan, J. L.; Waterhouse, A. L. and Williamson, G. (2008). Cocoa and health: A decade of research. British Journal of Nutrition, **99**(1):1-11. https://doi.org/10.1017/S0007114507795296

Daglia, M. (2012). Polyphenols as antimicrobial agents. Current Opinion in Biotechnology, **23**(2):174-181. https://doi.org/10.1016/j.copbio. 2011.08.007

Da-Silva, M.; Jaggers, G. K.; Verstraeten, S. V.; Erlejman, A. G.; Fraga, C. G. and Oteiza, P. I. (2012). Large procyanidins prevent bile-acid-induced oxidant production and membrane-initiated ERK1/2, p38, and Akt activation in Caco-2 cells. Free Radical Biology and Medicine, **52**(1):151-159. https://doi.org/10.1016/j.freeradbiomed. 2011.10 .436

Edo, G.; Onoharigho, F.; Emakpor, O. and Akpoghelie, P. (2022). The physicochemical analysis and health benefits of fresh and branded honey produced in delta state, Nigeria. J. Anal. Pharm Res., **11**(2):66-72. DOI: 10.15406/japlr.2022.11.00403

Ellam, S. and Williamson, G. (2013). Cocoa and human health. Annual Review of Nutrition, **33**(1):105-128.https://doi.org/10.1146/annurev-nutr-071811-150642

Erhonyota, C.; Edo, G. I. and Onoharigho, F. O. (2023). Comparison of poison plate and agar well diffusion method determining the antifungal activity of protein fractions. Acta Ecologica Sinica, **43**(4):684-689. https://doi.org/10.1016/j.chnaes.2022.08.006

Erlejman, A. G.; Jaggers, G.; Fraga, C. G. and Oteiza, P. I. (2008). TNF α-induced NF-êB activation and cell oxidant production are modulated by hexameric procyanidins in Caco-2 cells. Archives of Biochemistry and Biophysics, **476**(2):186-195. https://doi.org/10.1016/j.abb.2008.01.024

Gabrielsen, J. and Tanrikut, C. (2016). Chronic exposures and male fertility: the impacts of environment, diet, and drug use on spermatogenesis. Andrology, **3**(4):648-661. https://doi.org/10.1111/andr.12198

Goya, L.; Kongor, J. E. and Pascual-Teresa, S. (2022). From cocoa to chocolate: Effect of processing on flavanols and methylxanthines and their mechanisms of action. International Journal of Molecular Sciences. **23**(22):14365. https://doi.org/10.3390/ijms232214365

Hassan, M. U.; Chattha, M. U.; Khan, I.; Chattha, M. B.; Barbanti, L. and Aamer, M. (2021). Heat stress in cultivated plants: Nature, impact, mechanisms, and mitigation strategies: A review. Plant Biosystems-An International Journal Dealing with all Aspects of Plant Biology, **155**(2):211-234. https://doi.org/10.1080/11263504.2020.1727987

Hernandez Hernandez, C.; Morales Sillero, A.; Fernandez Bolanos, J.; Bermudez Oria, A.; Morales, A. A. and Rodriguez Gutierrez, G. (2019). Cocoa bean husk: Industrial source of antioxidant phenolic extract. Journal of the Science of Food and Agriculture, **99**(1):325-333. https://doi.org/10.1002/jsfa.9191

Hu, M. (2007). Commentary: Bioavailability of flavonoids and polyphenols: Call to arms. Molecular Pharmaceutics, **4**(6):803-806.https://doi.org/10.1021/mp7001363

Hussain, T.; Tan, B.; Yin, Y.; Blachier, F.; Tossou, M. C. and Rahu, N. (2016). Oxidative stress and inflammation: what polyphenols can do for us Oxidative Medicine and Cellular Longevity, **6**(1):7432797. https://doi.org/10.1155/2016/7432797

Jokic, S.; Gagic, T.; Knez, Z.; Subaric, D. and Skerget, M. (2018). Separation of active compounds from food by-product (cocoa shell) using subcritical water extraction. Molecules, **23**(6):1408. https://doi.org/10.3390/molecules23061408

Knapp, A. W. and Coward, K. H.(1935). The vitamin D activity of cacao shell: the effect of the fermenting and drying of cacao on the vitamin D potency of cacao shell. II. The origin of vitamin D in cacao shell. Biochemical Journal, **29**(12):27-28. doi: 10.1042/bj0292728

Kofink, M.; Papagiannopoulos, M. and Galensa R. (2007). Catechin in cocoa and chocolate: occurence and analysis of an atypical flavan-3-ol enantiomer. Molecules, **12**(7):1274-1288. https://doi.org/10.3390/12071274

Lecumberri, E.; Mateos, R.; Izquierdo-Pulido. M.; Ruperez, P.; Goya, L. and Bravo, L. (2007). Dietary fibre composition, antioxidant capacity and physico-chemical properties of a fibre-rich product from cocoa (*Theobroma cacao* L.). Food Chemistry,**104**(3):948-954. https://doi.org/10.1016/j.foodchem.2006.12.054

Lee, K. W.; Kim, Y. J.; Lee, H. J. and Lee, C. Y. (2003). Cocoa has more phenolic phytochemicals and a higher antioxidant capacity than teas and red wine. Journal of Agricultural and Food Chemistry, **51**(25):7292-7295. https://doi.org/10.1021/jf0344385

Manju, P. and Pushpa, A. (2020). Phytochemical analysis and in vitro free radical scavenging activity of rhizome of *Zingiber officinale* Rosc. Ann. Phytomed., **9**(2):257-262. http://dx.doi.org/10.21276/ap.2020.9.2.24

Martin, M. A.; Goya, L. and Ramos, S. (2013). Potential for preventive effects of cocoa and cocoa polyphenols in cancer. Food and Chemical Toxicology, **56**(5):336-351. https://doi.org/10.1016/j.fct.2013.02.020

Martin, M. A.; Goya, L. and Ramos, S. (2016). Preventive effects of cocoa and cocoa antioxidants in colon cancer. Diseases, **4**(1):6-10. https://doi.org/10.3390/diseases4010006

Martin Cabrejas, M. A.; Valiente, C.; Esteban, R. M.; Molla, E. and Waldron, K. (1994). Cocoa hull: A potential source of dietary fibre. Journal of the Science of Food and Agriculture, **66**(3):307-311. https://doi.org/10.1002/jsfa.2740660307.

Martinez, R.; Torres, P.; Meneses, M.; Figueroa, J.; Perez-Alvarez, J. and Viuda-Martos, M. (2012). Chemical, technological and *in vitro* antioxidant properties of cocoa (*Theobroma cacao* L.) co-products. Food Research International, **49**(1):39-45. https://doi.org/10.1016/j.foodres.2012.08.005

Martinez-Pinilla, E.; Onatibia-Astibia, A. and Franco, R. (2015). The relevance of theobromine for the beneficial effects of cocoa consumption. Frontiers in Pharmacology, **6**(10):126-866. https://doi.org/10.3389/fphar.2015.00030

Melo, T. S.; Pires, T. C.; Engelmann, J. V. P.; Monteiro, A. L. O.; Maciel, L. F. and Bispo, E. S.(2021). Evaluation of the content of bioactive compounds in cocoa beans during the fermentation process. Journal of Food Science and Technology, **58**(7):1947-1957. https://doi.org/10.1007/s13197-020-04706-w

Mollea, C.; Chiampo, F. and Conti, R. (2008). Extraction and characterization of pectins from cocoa husks: A preliminary study. Food Chemistry, **107**(3):1353-1356. https://doi.org/10.1016/j.foodchem. 2007.09.006

Nas, F.; and Ali, M.(2017). Phytochemical screening and antibacterial activity of *Azadiracta indica* stem and leaf extracts on *Escherichia coli* and *Staphylococcus aureus* isolated from spoiled cabbage. Journal of Pharmaceutical and Allied Sciences, **14**(4):2616-2624

Nazaruddin Ramli, N. R. and Asmawati, A. (2011). Effect of ammonium oxalate and acetic acid at several extraction time and pH on some physicochemical properties of pectin from cocoa husks (*Theobroma cacao*). African Journal of Food Science, **10**(3):790-798.

Nehlig, A. (2013). The neuroprotective effects of cocoa flavanol and its influence on cognitive performance. British Journal of Clinical Pharmacology, **75**(3):716-727. https://doi.org/10.1111/j.1365-2125.2012.04378.x

Nsor-Atindana, J.; Zhong, F. and Mothibe, K. J.(2012).*In-vitro* hypoglycemic and cholesterol lowering effects of dietary fiber prepared from cocoa (*Theobroma cacao* L.) shells. Food and Function, **3**(10):1044-1050. https://doi.org/10.1039/C2FO30091E

Nwosu, L. C.; Edo, G. I. and Ozgor, E.(2022). The phytochemical, proximate, pharmacological, GC-MS analysis of Cyperus esculentus (Tiger nut): A fully validated approach in health, food and nutrition. Food Bioscience, **46**:101-151. https://doi.org/10.1016/j.fbio.2022.101551

Ogunsipe, M.; Balogun, K.; Oladepo, A.; Ayoola, M. and Arikewuyo, M. (2017). Nutritive value of cocoa bean shell meal and its effect on growth and haematology of weaning rabbits. Nigerian Journal of Agriculture, Food and Environment, **13**(1):23-28.

Okiyama, D. C.; Soares, I. D.; Cuevas, M. S.; Crevelin, E. J.; Moraes, L. A. and Melo, M. P. (2018). Pressurized liquid extraction of flavanols and alkaloids from cocoa bean shell using ethanol as solvent. Food Research International, **114**(10):20-29. https://doi.org/10.1016/j.foodres.2018. 07.055.

Okiyama, D. C.; Soares, I. D.; Toda, T. A.; Oliveira, A. L. and Rodrigues, C. E.(2019). Effect of the temperature on the kinetics of cocoa bean shell fat extraction using pressurized ethanol and evaluation of the lipid fraction and defatted meal. Industrial Crops and Products, **130**(10):96-103. https://doi.org/10.1016/j.indcrop.20 18.12.063

Onyibe, P. N.; Edo, G. I.; Nwosu, L. C. and Ozgor, E.(2021). Effects of vernonia amygdalina fractionate on glutathione reductase and glutathione-S-transferase on alloxan induced diabetes wistar rat. Biocatalysis and Agricultural Biotechnology, **36**(9):102-118. https://doi.org/10.1016/j.bcab.2021.102118

Osundahunsi, O.; Bolade, M. and Akinbinu, A. (2007). Effect of cocoa shell ash as an alkalizing agent on cocoa products. Journal of Applied Sciences, **7**(10):1674-1678.

Papillo, V. A.; Locatelli, M.; Travaglia, F.; Bordiga, M.; Garino, C.; Coisson, J. D. and Arlorio, M.(2019). Cocoa hulls polyphenols stabilized by microencapsulation as functional ingredient for bakery applications. Food Research International, **115**(6):511-518. https://doi.org/10.1016/j.foodres.2018.10.004

Perez, E.; Mendez, A.; Leon, M.; Hernandez, G. and Sivoli, L.(2015). Proximal composition and the nutritional and functional properties of cocoa by-products (pods and husks) for their use in the food industry. Cocoa By-Prod. Technol Rheol Styl Nutr., **2**(10):219-234

Perez-Santana, D.; Rodriguez-Sanchez, J. L.; Calle, J.; De Villavicencio, M. N.; Diaz-Ortega, L. and Herrera-Llanes L. (2018). Utilización de la cascarilla de cacao como fuente de fibra dietética y antioxidantes en la elaboración de galletas dulces: Use of cocoa bean shell as a source of dietetic fiber and antioxidants in the production of sweet cookies. Ciencia y Tecnologia de Alimentos,**28**(3):62-67.

Rahul, R.; Zade. and Anita, Wanjari. (2023). Anti-inflammatory activity of *Ricinus communis* L.: A systematic review. Ann. Phytomed., **12**(1):51-55. http://dx.doi.org/10.54085/ap.2023.12.1.46.

Ramos, S.; Rodriguez-Ramiro, I.; Martin, M. A.; Goya, L. and Bravo, L. (2011). Dietary flavanols exert different effects on antioxidant defenses and apoptosis/proliferation in Caco-2 and SW480 colon cancer cells. Toxicology *in vitro*, **25**(8):1771-1781. https://doi.org/10.1016/j.tiv.2011.09.007

Rani, V.; Bhatia, A. and Kaushik, R. (2021). Inoculation of plant growth promoting-methane utilizing bacteria in different N-fertilizer regime influences methane emission and crop growth of flooded paddy. Science of The Total Environment,**775**(10):145-826.https://doi.org/10.1016/j.scitotenv.2021.145826.

Redgwell, R.; Trovato, V.; Merinat, S.; Curti, D.; Hediger, S. and Manez, A. (2003). Dietary fibre in cocoa shell: Characterisation of component polysaccharides. Food Chemistry, **81**(1):103-112. https://doi.org/10.1016/S0308-8146(02)00385-0

Reed, S. (2010). Sensory analysis of chocolate liquor. Manufacturing Confectioner, **90**(10):43-52.

Rodriguez-Mateos, A.; Vauzour, D.; Krueger, C. G.; Shanmuganayagam, D.; Reed, J. and Calani, L. (2014). Bioavailability, bioactivity and impact on health of dietary flavonoids and related compounds: An update. Archives of Toxicology, **88**(2):1803-1853. https://doi.org/10.1007/s00204-014-1330-7

Rodriguez-Ramiro, I.; Martin, M. A.; Ramos, S.; Bravo, L. and Goya, L. (2011). Comparative effects of dietary flavanols on antioxidant defences and their response to oxidant induced stress on Caco2 cells. European Journal of Nutrition, **50**(13):313-322. https://doi.org/10.1007/s00394-010-0139-2

Rodriguez-Ramiro, I.; Ramos, S.; Bravo, L.; Goya, L. and Martin, M. A. (2011). Procyanidin B2 and a cocoa polyphenolic extract inhibit acrylamide-induced apoptosis in human Caco-2 cells by preventing oxidative stress and activation of JNK pathway. The Journal of Nutritional Biochemistry, **22**(12):1186-1194. https://doi.org/10.1016/j.jnutbio.2010.10.005

Rodriguez-Ramiro, I.; Ramos, S.; Lopez-Oliva, E.; Agis-Torres, A.; Bravo, L.; Goya, L. and Martin, M. A. (2013). Cocoa polyphenols prevent inflammation in the colon of azoxymethane-treated rats and in TNF-α-stimulated Caco-2 cells. British Journal of Nutrition, **110**(2):206-215. https://doi.org/10.1017/S0007114512004862

Rojo-Poveda, O.; Barbosa-Pereira, L.; Mateus-Reguengo, L.; Bertolino, M.; Stevigny, C. and Zeppa, G. (2019). Effects of particle size and extraction methods on cocoa bean shell functional beverage. Nutrients, **11**(4):867-869. https://doi.org/10.3390/nu11040867

Romier-Crouzet, B.; Van-De-Walle, J.; Joly, A.; Rousseau, C. and Henry, O. (2009). Inhibition of inflammatory mediators by polyphenolic plant extracts in human intestinal Caco-2 cells. Food and Chemical Toxicology, **47**(6):1221-1230. https://doi.org/10.1016/j.fct.2009.02.015

Rossin, D.; Barbosa-Pereira, L.; Iaia, N.; Testa, G.; Sottero, B. and Poli, G. (2019). A dietary mixture of oxysterols induces *in vitro* intestinal inflammation through TLR2/4 activation: The protective effect of cocoa bean shells. Antioxidants, **8**(6):151-156. https://doi.org/10.3390/antiox8060151

Rudrapal, M.; Khairnar, S. J.; Khan, J.; Dukhyil, A. B.; Ansari, M. A. and Alomary, M. N. (2022). Dietary polyphenols and their role in oxidative stress-induced human diseases: Insights into protective effects, antioxidant potentials and mechanism (s) of action. Frontiers in Pharmacology, **13**(5):806470. https://doi.org/10.3389/fphar.2022.806470

Rusconi, M. and Conti, A. (2010). *Theobroma cacao* L., the Food of the Gods: A scientific approach beyond myths and claims. Pharmacological Research, **61**(1):5-13. https://doi.org/10.1016/j.phrs.2009.08.008

Saman, H.; Raza, SS.; Uddin, S. and Rasul, K. (2020). Inducing angiogenesis, a key step in cancer vascularization, and treatment approaches. Cancers, **12**(5):11-72. https://doi.org/10.3390/cancers12051172

Samanta, S.; Sarkar, T.; Chakraborty, R.; Rebezov, M. and Shariati, M. A. (2022). Thiruvengadam M, Rengasamy KR. Dark chocolate: An overview of its biological activity, processing, and fortification approaches. Current Research in Food Science, **5**(6):1916-1943. https://doi.org/10.1016/j.crfs.2022.10.017

Sandoval, A. J.; Barreiro, J. A.; De-Sousa, A.; Valera, D.; Lopez, J. V. and Muller, A. J. (2019). Composition and thermogravimetric characterization of components of Venezuelan fermented and dry Trinitario cocoa beans (*Theobroma cacao* L.): Whole beans, peeled beans and shells. Revista Técnica de la Facultad de Ingeniería, Universidad del Zulia, **42**(1):39-46. https://doi.org/10.22209/rt.v42n1a06

Sanjeev Singh and Divya Singh (2021). Phytomedicine: Alternative safe vehicles on the pathway of diabetes mellitus. Ann. Phytomed., **10**(1):114-122.

Sies, H.; Schewe, T.; Heiss, C. and Kelm, M. (2005). Cocoa polyphenols and inflammatory mediators. The American Journal of Clinical Nutrition, **81**(1):304-312. https://doi.org/10.1093/ajcn/81.1.304S

Soares, T. F. and Oliveira, M. B .P. (2022). Cocoa by-products: Characterization of bioactive compounds and beneficial health effects. Molecules, **27**(5):16-25. https://doi.org/10.3390/molecules27051625

Sreenivasagan, S.; Subramanian, A. K. and Rajeshkumar, S.(2020). Assessment of antimicrobial activity and cytotoxic effect of green mediated silver nanoparticles and its coating onto mini-implants. Ann. Phytomed., **9**(1):207-212. http://dx.doi.org/10.21276/ap.2020.9.1.27.

Subramaniam, S.; Selvaduray, K. R. and Radhakrishnan, A. K. (2019). Bioactive compounds: natural defense against cancer. Biomolecules, **9**(12):758-762. https://doi.org/10.3390/biom9120758

Tan, X.; Hu, D.; Li, S.; Han, Y.; Zhang, Y. and Zhou, D. (2000). Differences of four catechins in cell cycle arrest and induction of apoptosis in LoVo cells. Cancer Letters, **158**(1):1-6. https://doi.org/10.1016/S0304-3835(00)00445-6

Vaidya, S.N.; Telrandhe U.B and Agrawal S. (2022). Nutritional and health benefits of kiwifruit: An overview. Ann. Phytomed., **11**(2):176-185. http://dx.doi.org/10.54085/ap.2022.11.2.19.

Vauzour, D. (2014). Effect of flavonoids on learning, memory and neurocognitive performance: relevance and potential implications for Alzheimer's disease pathophysiology. Journal of the Science of Food and Agriculture, **94**(6):1042-1056. https://doi.org/10.1002/jsfa.6473

Vojvodic, A.; Komes, D.; Vovk, I.; Belccak-Cvitanovi, A. and Busic, A. (2016). Compositional evaluation of selected agro-industrial wastes as valuable sources for the recovery of complex carbohydrates. Food Research International, **89**(15):565-573. https://doi.org/10.1016/j.foodres.2016.07.023

Wollgast, J. and Anklam, E.(2000). Review on polyphenols in *Theobroma cacao*: Changes in composition during the manufacture of chocolate and methodology for identification and quantification. Food Research International, **33**(6):423-447. https://doi.org/10.1016/S0963-9969(00)00068-5

Zeng, W.; Zeng, Z.; Teng, J.; Rothenberg, D.; Zhou, M. and Lai, R. (2022). Comparative analysis of purine alkaloids and main quality components of the three Camellia species in China. Foods, **11**(5):627-630. https://doi.org/10.3390/foods11050627

Citation **J. Rajangam, M. Kabilan, R.V. Sundarrajan, V. Raja, M. Thangamuniyandi, C. Sankar and P. M. Usha Nandhini (2025). A comprehensive review on nutraceutical properties and pharmacological benefits for human healthcare in cocoa (*Theobroma cacao* L.). Ann. Phytomed., 14(1):115-127. http://dx.doi.org/10.54085/ap.2025.14.1.12.**